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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,509	08/29/2006	Duncan Hiscock	PZ0386	5657

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Amersham Health Inc
IP Department
101 Carnegie Center
Princeton, NJ 08540

EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	PAPER NUMBER
1618	

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04/26/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,509	HISCOCK ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,14,17,18,26-28,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,14,17,18,26-28,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 1/25/2010, in reply to the Office Action mailed 8/25/2009, is acknowledged and has been entered. Claims 1, 17, 26 and 31 have been amended. Claims 2, 4-13, 15, 16, 19-25 and 29 have been cancelled. Claims 1, 3, 14, 17, 18, 26-28, 30 and 31 are pending and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Applicant's arguments have been fully considered but are not persuasive for reasons set forth hereinbelow.

Double Patenting

Claims 1, 3, 14, 17, 18, 26-28, 30 and 31 are provisionally rejected on the grounds of obviousness-type double patenting over the claims of copending Application Serial No. 11/815,360 for reasons set forth in the previous Office Action.

Applicant argues on page 12 of the Response that a terminal disclaimer will be filed in the event that the '360 Application is allowed.

No terminal disclaimer has been received at this time, accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 14, 17-18, 26-28 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (*J. Biol. Chem.*, 2000, 275(21), p. 16007-16014), in view of Haberkorn *et al.* (*Nuclear Medicine and Biology*, 2001, 28(7) p. 793-798) and Colucci *et al.* (US 2006/0069038), further in view of Flanagan (US 5,601,801), for reasons set forth in the previous Office Action.

Applicant argues on pages 9-11 of the Response that Haberkorn very clearly teaches in conclusion that the caspase inhibitor approach is not suitable for imaging purposes - and that a caspase substrate should be successful. Based on Haberkorn read at the priority date of the present invention, the person skilled in the art could have no motivation to prepare further radiolabeled caspase inhibitors. Haberkorn provides a clear teaching instead towards labeled caspase substrates. Haberkorn thus teaches away from he present invention. In addition, the combination of references suggested by the Examiner is believed invalid, since it contradicts the clear teaching of Haberkorn itself against further use of the inhibitor approach. Applicant further argues

that Colucci does not teach in vivo imaging using PET or SPECT as required by present amended claim 1. In addition, the teaching of Colucci is limited only to the isotope ^{125}I, which is outside the scope of revised claim 1.

This is not found to be persuasive. Haberkorn teaches that the concentration of activated caspases is unknown and that irreversible binding results in the consumption of the sites and that the use of a caspase inhibitor results in trapping of one tracer per activated caspase. However, the isatin sulfonamide inihibitors, such as compound 3, shown by Lee are reversible inhibitors (page 16009-16010), and thus would not feature the problem associated with irreversible binding disclosed by Haberkorn, especially considering the favorable K_i of the Lee compounds with respect to substrate concentration. Colucci teaches that ^{125}I-M808 detects active caspases in vivo (see paragraph 0274). One of ordinary skill could have readily substituted ^{123}I, ^{124}I for ^{131}I or ^{125}I, as shown by Flanagan.

New Grounds for Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee *et al.*, (*J. Biol. Chem.*, 2000, 275(21), p. 16007-16014).

Lee discloses sulfonyl isatin compounds of formula (I) and the novel inhibition of caspases for use in treatment of apoptosis, and disease states caused by excessive or inapropriate cell death (abstract) and column 5. The compounds are isatin sulfonamide derivatives, such as compounds 3 and 4 having K_i = 60 and 15 nM, respectively. The claims require only that the precursor is "capable of" reaction with radioactive non-metal or halogen. With regard to the limitation that the non-radioactive derivative is chosen from a-e, it is noted that the isatin sulfonamide compound 3 contains an amine on the isatin ring, which is capable of facile alkylation, see for example at the alkylated nitrogen in compound 4.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

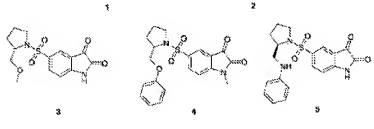
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 14, 17-18, 26-28, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (*J. Biol. Chem.*, 2000, 275(21), p. 16007-16014), in view of Haberkorn *et al.* (*Nuclear Medicine and Biology*, 2001, 28(7) p. 793-798) and Colucci *et al.* (US 2006/0069038), further in view of Flanagan (US 5,601,801) and Hunter (US 7,018,610).

Lee discloses potent and selective nonpeptide inhibitors of caspase 3 and 7 which inhibit apoptosis and maintain cell functionality (page 16007). See Figure 1. The compounds are isatin sulfonamide derivatives, such as compounds 3 and 4 having K_i = 60 and 15 nM, respectively. These inhibitors blocked apoptosis in murine bone marrow neutrophils and human chondrocytes. Furthermore, in camptothecin-induced chondrocyte apoptosis, cell functionality as measured by type II collagen promoter activity is maintained, an activity considered essential for cartilage homeostasis. These data suggest that inhibiting chondrocyte cell death with a caspase 3/7-selective inhibitor may provide a novel therapeutic approach for the prevention and treatment of osteoarthritis, or other disease states characterized by excessive apoptosis (abstract).



Lee does not specifically recite radiolabeled 2-oxindole sulphonamide caspase-3 inhibitors.

Haberkorn discloses that caspases, once activated, play a key role in the intracellular signal cascade of cells undergoing apoptosis, and performed experiments to evaluate cysteine proteases of the caspase family as targets for the trapping of radiolabeled Z-VAD-fmk [benzyloxycarbonyl-Val-Ala-DL-Asp(O-methyl)-fluoromethyl ketone]. Z-VAD-fmk is an irreversible inhibitor of the cysteine protease intedeukin-l/3 converting enzyme (ICE) and was chosen, because it is successfully used as a pan-caspase inhibitor in apoptosis research. The study was undertaken to label Z-VAD-fmk with radioiodine at the phenyl moiety of the N-terminal Z-protection group and to assess the cellular uptake of IZ-VAD-fmk in apoptotic versus control cells (page 794). Radioiodinated Z-Val-Ala-DL-Asp(0-methyl)-fluoromethyl ketone, [^{131}I]IZ-VAD-fmk, as a potential apoptosis imaging agent (abstract). A solution of [^{131}I]IZ-VAD-fmk in PBS containing 10% EtOH is disclosed (page 794, right column). ^{131}I is attached to Z-VAD-fmk through electrophilic substitution of the benzene ring (page 795). Activated caspases play a key role in the intracellular signal cascade of cells undergoing apoptosis. Therefore, these enzymes could serve as targets for the binding of radiolabeled substrates which in turn exhibit potential for the imaging of apoptotic cells. Z-VAD-fmk, an irreversibly binding pan-caspase inhibitor, was selected for labeling and biological testing in apoptotic cells assuming that caspase inhibitors selectively bind to activated caspases resulting in the trapping of their radiolabeled counterparts. This kind of trapping mechanism could be used for the non-invasive detection of apoptosis by the assessment of radiolabeled IZ-VAD-fmk accumulation. Furthermore, the measurement of activated caspases are thought to be more specific for the detection of apoptosis than

the annexin V approach where also necrotic cells may contribute to the signal. An approach based on the visualization of caspase activation may detect early stages of apoptosis (797).

Colucci discloses compounds of Formula I useful as caspase active site probes. These probes can be used to determine whether a caspase has been activated, in cells or in tissues of animal models of various pathologies (paragraph 0003). See Figure 3, potency assessment caspase inhibitors by [^{125}I]-M808 labeling and by DEVD-AMC cleavage activity. Under the fluorogenic assay conditions K_i=$IC_{50/2}$ (paragraph 0006). Any suitable route of administration may be employed for providing a dosage of a compound of the present invention. For example, oral, parenteral and topical may be employed (paragraph 0228). Pharmaceutical carriers are disclosed (paragraph 0231-0232). See also synthetic methods in paragraph 0233 (e.g. $SnBu_3$ substitution).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide an iodine radiolabel on the 2-oxindole sulphonamide3 caspase-3 inhibitors disclosed by Lee. One would have been motivated to do so because Haberkorn discloses that ^{131}I radiolabeled caspase-3 inhibitor IZ-VAD-fmk may be useful in imaging of apoptosis. Colucci also discloses ^{125}I radiolabeled caspase-3 inhibitors as apoptosis probes. One would have had a reasonable expectation of success in doing so because Lee teaches that his compounds are potent and selective non-peptide inhibitors of the effector caspases 3 and 7 and that the inhibition of apoptosis and maintenance of cell functionality with a caspase 3/7-selective inhibitor is demonstrated, suggesting that targeting these two caspases alone is sufficient for

blocking apoptosis. Accordingly, one of ordinary skill would have had a reasonable expectation of success in using the selective caspase-3 inhibitors of Lee as apoptosis probes, as was shown by Haberkorn and Colucci for other known caspase-3 inhibitors. Furthermore, one of ordinary skill would have recognized that compounds 4 and 5 of Lee have structural features that would render them capable of similar radiolabeling procedures that were used in Haberkorn and/or Colucci (e.g. electrophilic substitution of the benzene ring). It would have been further obvious to provide the formulation in sterile form, since it is intended for intravenous administration, such as to minimize microbial infection, etc.

It would have been further obvious to provide ^{123}I radiolabeling when the teachings of Lee, Haberkorn and Colucci are taken in view of Flanagan.

Flanagan discloses angiotensin convening enzyme (ACE) inhibitors can be labelled with Iodine-123, Iodine-125, Iodine-127 or Iodine-131, useful to image the kidneys and lungs for diagnosis and treatment of diseases such as essential hypertension, renal artery stenosis, or diabetes which are associated with a change in the amount of ACE present in the human body (abstract, claim 1). Radiolabelled derivatives of lisinopril are labeled with Iodine-123, Iodine-125, Iodine-127 or Iodine-131 on the 2, 3, or 4 position of the phenyl ring (column 2, lines 5+). It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute ^{123}I as a functionally equivalent gamma-emitting radionuclide for ^{131}I or ^{125}I in the radiolabeled caspase-3 inhibitors of Haberkorn or Colucci, respectively. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-

97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (^{123}I, ^{131}I or ^{125}I) and their functions were known in the art at the time of the instant invention. One of ordinary skill in the art could have substituted one known gamma emitting radioactive iodine radionuclide for another, and the results of the substitution would have been predictable, that is SPECT imaging of apoptosis using a radiolabeled caspase-3 inhibitor.

It would have been further obvious to perform radiolabeling using compounds conjugated to solid support when the teachings of Lee, Haberkorn, Colucci and Flanagan are taken in view of Hunter.

Hunter discloses that molecules labeled with radioactive isotopes have been used as both imaging agents in medical diagnosis as well as therapeutic agents in the treatment of cancer. Both radiolabeled small molecules and radiolabeled peptides and nucleotides have been used to diagnose tumors. One common method of labeling molecules with radioactive isotopes for medical use is a stannylation process. While this process yields isotopically pure products, toxic tin by-products remain and must be separated before the radiolabeled molecules can be used. Furthermore, the unstable nature of radiolabeled molecules and their precursors lead to a short shelf life. Hunter's

invention is directed to compounds that may be used to prepare radiolabeled compounds in an effective manner. The invention is also directed in part to methods of reparing radiolabeled compounds. One aspect of the present invention relates to polymer precursor compounds represented by: Poly--L--R—Y (column 1-2). A further aspect contemplates a kit including subject compounds, and optionally instructions for their use. Uses for such kits include therapeutic and medical imaging applications. In one embodiment, a kit containing a radiolabeling system is provided, which comprises a polymer precursor compound and instructions for using said polymer precursor compound, wherein said polymer precursor compound comprises the polymer precursor compound shown in structure 1. In a further embodiment, the kit includes a filter or a filtration device. Certain compounds of the invention are precursors for the rapid and efficient radiolabeling of compounds. Since radiolabeled compounds may have a very short shelf life, a stable precursor may be needed for storage until use. Another aspect relates to methods of synthesizing isotopically pure radiolabeled compounds without unwanted impurities (column 3, lines 20+).

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform radiolabeling using compounds conjugated to solid support, and one would have been motivated to do so because Hunter teaches that such methods provide known advantages such as reduced toxicity byproducts, improved product purity, improved shelf-life of radiopharmaceuticals. Furthermore, Hunter's methods include solid-supported stannylation processes, and both Haberkorn and Colucci employ stannylation in their radiosynthesis.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS